

Clinical factors related to recurrence after hepatic arterial concurrent chemoradiotherapy for advanced but liver-confined hepatocellular carcinoma

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Before the sorafenib era, advanced but liver-confined hepatocellular carcinoma (HCC) was treated by liver-directed therapy. Hepatic arterial concurrent chemoradiotherapy (CCRT) has been performed in our group, giving substantial local control but frequent failure. The aim of this study was to analyze patterns of failure and find out predictive clinical factors in HCC treated with a liver-directed therapy, CCRT. A retrospective analysis was done for 138 HCC patients treated with CCRT between May 2001 and November 2009. Protocol-based CCRT was performed with local radiotherapy (RT) and concurrent 5-fluorouracil (5-FU) hepatic arterial infusion chemotherapy (HAIC), followed by monthly HAIC (5-FU and cisplatin). Patterns of failure were categorized into three groups: infield, intrahepatic-outfield and extrahepatic failure. Treatment failure occurred in 34.0% of patients at 3 months after RT. Infield, intrahepatic-outfield and extrahepatic failure were observed in 12 (8.6%), 26 (18.7%) and 27 (19.6%) patients, respectively. Median progression-free survival for infield, outfield and extrahepatic failure was 22.4, 18 and 21.5 months, respectively. For infield failure, a history of pre-CCRT treatment was a significant factor ($P=0.020$). Pre-CCRT levels of alpha-fetoprotein and prothrombin induced by vitamin K absence or antagonist-II were significant factors for extrahepatic failure ($P=0.029$). Treatment failures after CCRT were frequent in HCC patients, and were more commonly intrahepatic-outfield and extrahepatic failures than infield failure. A history of pre-CCRT treatment and levels of pre-CCRT tumor markers were identified as risk factors that could predict treatment failure. More intensified treatment is required for patients presenting risk factors.

Keywords: hepatocellular carcinoma; hepatic arterial concurrent chemoradiotherapy (CCRT); patterns of failure; risk factors

INTRODUCTION

The Barcelona Clinic Liver Cancer (BCLC) treatment guidelines divide patients diagnosed with hepatocellular carcinoma (HCC) into very early, early, intermediate, advanced and terminal stages [1]. While very early and early-stage patients would be candidates for curative therapy, those with intermediate or advanced stage are not. Unfortunately, more than 80% of HCC patients are diagnosed at an advanced stage, with poor prognosis and a lack of effective therapies.

Recently, a multicenter, randomized, double-blind, placebo-controlled, phase 3 trial in western countries [2] has shown that the median overall survival and time to progression of patients treated with sorafenib were nearly 3 months longer than for placebo treatment. The positive sorafenib finding has also been observed in the Asian-Pacific population [3]. Thus, the BCLC staging classification and treatment strategy recommends sorafenib as a standard treatment of advanced HCC.

The BCLC advanced stage involves a wide spectrum of diseases: vascular invasion (portal vein thrombosis), lymph

node metastasis, distant metastasis, and mildly symptomatic performance status (Eastern Cooperative Oncology Group Grade 1/2). Although sorafenib is a standard of care, its limited benefit urges further investigation of new approaches. Particularly in liver-confined disease, a liver-directed therapy is worth serious consideration.

Before the introduction of sorafenib, our group developed a protocol-based hepatic arterial concurrent chemoradiotherapy (CCRT) consisted of local radiotherapy (RT) and concurrent 5-fluorouracil (5-FU) hepatic arterial infusion chemotherapy (HAIC), followed by monthly HAIC (5-FU and cisplatin) for 6 months. Even though sorafenib was introduced to medical practice in 2009, its high cost has been a major barrier to routine clinical use in Korea. Therefore CCRT has continued to be used in our clinic.

A pilot trial reported in 2008 showed a response rate of 45%, a 3-year overall survival rate of 24.1%, and a median survival time of 13.1 months, which exceeds the previously reported 6 months more than 2-fold [4]. This encouraged us to continue this protocol-based CCRT. However, the results are still unsatisfactory due to frequent failure. Intrahepatic-outfield and extrahepatic metastases were frequently seen after CCRT. To improve the therapeutic outcome of HCC patients treated with CCRT, better understanding of patterns of treatment failure is prerequisite. In this study, we aimed to analyze patterns of failure and to find out predictive clinical factors in HCC treated with a liver-directed therapy of CCRT.

MATERIALS AND METHODS

Medical records of 138 HCC patients treated with CCRT in Severance hospital between May 2001 and November 2009 were reviewed retrospectively. As yet, sorafenib has not been introduced to routine medical practice in Korea.

The patient, tumor and treatment characteristics of the study group are shown in Table 1. The median patient age was 55 years (range, 33–79 years), and the ratio of males to females was 7:1. The median follow-up period was 36 months for all patients. The number of patients with modified International Union Against Cancer (UICC) Stage T3N0M0 and T4N0M0 was 24 (17.4%) and 86 (62.3%), respectively. While CCRT was applied to locally advanced HCC with T3 and T4 stage, 20 patients (14.5%) with T2 stage were also included due to large tumors of ~10 cm. Portal vein thrombosis was observed in 77 patients (55.8%). A total of 104 patients (75.4%) were newly diagnosed as HCC (primary treatment group), and 34 patients (24.6%) had been treated with another treatment modality before CCRT (recurrence treatment group). Transarterial chemoembolization (TACE) was the most common treatment before CCRT.

The CCRT protocol in our institution consists of CCRT followed by hepatic arterial chemotherapy, as described in our

previous study [4]. Before CCRT was started, a percutaneous hepatic arterial catheter (chemoport) was inserted, then drug distribution was simulated by hepatic angiography through the chemoport. Concurrent continuous-infusion hepatic arterial 5-FU (at a dose of 500 mg/day) was delivered during the first and last weeks of RT through the chemoport. One month after CCRT, HAIC with 5-FU (at a dose of 500 mg/m² for 5 h on Days 1–3) and cisplatin (at a dose of 60 mg/m² for 2 h on Day 2) were administered every 4 weeks for 3–12 cycles, according to tumor response; these courses are termed ‘repeated HAIC’. Repeated HAIC was stopped if disease progression was shown.

Three-dimensional conformal radiotherapy (3D-CRT) was performed on 81.9% of patients, and intensity-modulated radiotherapy was applied in the remaining 18.1%. The median radiation dose was 45 Gy (range, 45–64.8 Gy), and the median dose per fraction was 1.8 Gy (range, 1.8–2.95 Gy).

The median pre-CCRT serum level of the liver tumor marker alpha-fetoprotein (AFP) was 570.4 IU/ml (range, 1.0–88 336.5), and 78 patients had levels >200 IU/ml. The median pre-CCRT level of the second marker, prothrombin induced by vitamin K absence (PIVKA-II), was 1641 mAU/ml (range, 10.0–2000.0), and 118 patients had serum levels >60 mAU/ml.

Tumor responses were evaluated using modified Response Evaluation Criteria in Solid Tumors [5], defining the viable tumor by its uptake of contrast agent in the arterial phase of dynamic computed tomography or magnetic resonance imaging. The tumor response was categorized as complete response (CR), i.e. the disappearance of any intratumoral arterial enhancement in all targets; partial response (PR), at least a 30% decrease in the sum of diameters of viable target lesions; progressive disease (PD), an increase of at least 20% in the sum of the diameters of viable target lesions; or as stable disease (SD), any cases that do not qualify for either PR or PD.

Patterns of failure were categorized into three groups: infield failure, intrahepatic-outfield failure, and extrahepatic failure. Infield failure was defined as progression of the tumor within the radiation field that covered the planning target volume. Intrahepatic failure was defined as progression of the tumor within the liver but outside of the radiation field. Extrahepatic failure refers to distant metastasis in lung, bone, etc.

Overall survival, progression-free survival (PFS), and clinical factors influencing each failure were analyzed using the Kaplan-Meier method. Multivariate analysis was performed using the Cox-proportional hazard model, and *P* values were calculated from the log-rank test.

RESULTS

Median follow-up time was 10.4 months (range, 0.4–92.4) in all patients and 35.2 months (range, 13.9–92.4) in surviving patients. The median overall survival time from the end of RT was 11.1 months, and the survival rates at 1 and 2 years

Table 1. Patient characteristics

Characteristics	No. of Patients (%)
Age (median year)	55 (range, 33–79)
< 50	37 (26.8)
≥ 50	101 (73.2)
Gender	
Male	120 (87.0)
Female	18 (13.0)
Viral type	
B	116 (84.1)
C	9 (6.5)
non-B, non-C	13 (9.4)
Child-Pugh class	
A	125 (90.6)
B	13 (9.4)
ICG R15 (median %)	10.8 (range, 1.4–70.9)
Modified UICC stage	
II	
T2N0M0	20 (14.5)
III	
T3N0M0	65 (47.1)
IVA	
T4N0M0	41 (29.7)
T2N1M0	1 (0.7)
T3N1M0	10 (7.2)
T4N1M0	1 (0.7)
Portal vein thrombosis	
No	61 (44.2)
Yes	77 (55.8)
Lymph node metastasis	
No	126 (91.3)
Yes	12 (8.7)
Pre-CCRT AFP (median IU/ml)	570.4 (range, 1.0–88 336.5)
< 200	60 (43.5)
≥ 200	78 (56.5)
Pre-CCRT PIKVA-II (median mAU/ml)	1641 (range, 10.0–2 000.0)
< 60	17 (12.6)
≥ 60	118 (87.4)
Pre-CCRT treatment history	
No (primary treatment group)	104 (75.4)

*Continued***Table 1.** *Continued*

Characteristics	No. of Patients (%)
Yes (recurrence treatment group)	34 (24.6)
Contents of pre-CCRT treatment	
TACE	19 (55.9)
TACE, internal RT (Holmium-166)	4 (11.8)
TACE, RFA	3 (8.8)
TACE, surgery	1 (2.9)
TACE, systemic chemotherapy ^a	1 (2.9)
TACE, internal RT (Holmium-166), Sorafenib	1 (2.9)
RFA	1 (2.9)
Intra-arterial chemotherapy ^b	2 (5.9)
Internal RT (Holmium-166)	1 (2.9)
Radiotherapy technique	
3D CRT	113 (81.9)
IMRT	25 (18.1)
Total dose (median Gy)	45.0 (range, 45.0–64.8)
Dose/fraction (median Gy)	1.8 (range, 1.8–3.0)

ICG = indocyanine green, UICC = International Union Against Cancer, CCRT = concurrent chemoradiotherapy, TACE = transarterial chemoembolization, RT = radiation therapy, RFA = radiofrequency ablation, AFP = alpha-feto-protein, PIVKA-II = protein induced by vitamin K absence, 3D CRT = three-dimensional conformal radiation therapy, IMRT = intensity-modulated radiation therapy.

^aSystemic adriamycin/cisplatin.

^bCisplatin 1, fluorouracil/cisplatin 1.

were 46.1% and 27.9%, respectively (Fig. 1). At the last follow-up, 115 patients (83.3%) had died, the status of 2 (1.4%) was unknown, and 21 (15.2%) were still alive. Of the patients who were alive, 16 patients had no evidence of disease, and five were living with disease. The median PFS for infield, intrahepatic-outfield and extrahepatic failures were 22.4, 18 and 21.5 months, respectively. The 1-year PFS rates for the same failure groups were 72.2, 62.1 and 56.6%, respectively.

The treatment response was evaluated at 3 months after finishing RT in the CCRT protocol (Table 2). Treatment failure occurred in 34.0% of the patients within 3 months after RT. Details of treatment failure are shown in Fig. 2. During the whole period of follow-up, treatment failure occurred in 106 patients (76.8%) and 46 patients (33.3%) had infield failure. Intrahepatic-outfield and extrahepatic failures were more common than infield failure. The sites of extrahepatic failure, in order of frequency, were lung, distant lymph

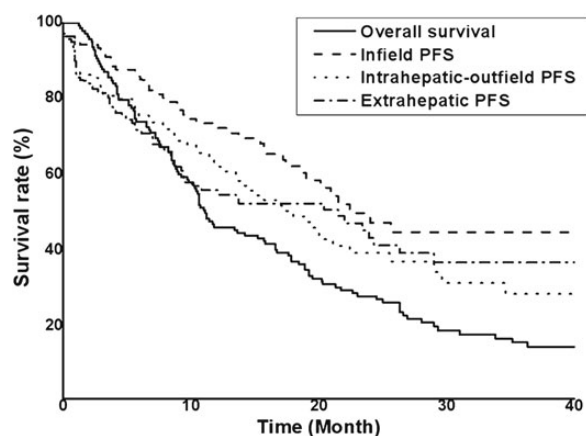


Fig. 1. Overall survival and progression-free survival curves. The 1-year survival rate was 46.1% and median overall survival (OS) was 11.1 months. Progression-free survival rates at 1 year after RT were 72.2%, 62.1%, and 56.6% for infield, intrahepatic-outfield, and extrahepatic failures, respectively. The median PFS for the same failure groups were 22.4, 18, and 21.5 months, respectively.

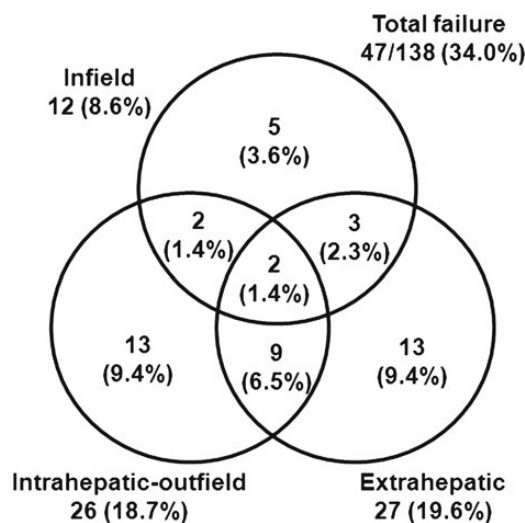


Fig. 2. Patterns of failure. Patterns of failure were categorized into three groups; infield, intrahepatic-outfield, and extrahepatic failures. At 3 months after concluding RT in the CCRT protocol, treatment failures occurred in 47 patients (34.0%).

Table 2. Treatment response at 3 months after radiotherapy

Response	No. (%)
Complete response	4 (2.9)
Partial response	77 (55.8)
Stable disease	45 (32.6)
Progressive disease	12 (8.7)

node, bone, peritoneal seeding, adrenal gland, pleura and brain.

About half of treatment failure was combined with other categories of failure such as infield with intrahepatic-outfield failure, or infield with extrahepatic failure; 7 of 12 infield failures, 13 of 26 intrahepatic-outfield failures, and 14 of 27 extrahepatic failures.

The association of clinical factors involving age, sex, stage, portal vein thrombosis, treatment history and pre-CCRT tumor marker level were analyzed by univariate and multivariate analysis for prognostic significance for PFS (Table 3 and Fig. 3). The PFS for infield failure was improved in patients in the primary treatment group compared with patients in the recurrence treatment group (at 2 years after RT, PFS of 53.5% vs 29.6%, $P=0.035$). Other clinical factors including T stage, tumor size and RT dose were not associated with local control. Both the elevation of pre-CCRT AFP levels (≥ 200 IU/ml) and PIVKA-II (≥ 60 mAU/ml) were significant factors for intrahepatic-outfield failure (at 2 years after RT, PFS 43.5% vs 38.7%, $P=0.005$). For extrahepatic failure, an age of <50 years was a significant factor ($P=0.007$), as were biomarker levels of AFP ≥ 200 IU/

ml and PIVKA-II ≥ 60 mAU/ml ($P=0.003$). In multivariate analysis, the levels of the two biomarkers were not associated with intrahepatic-outfield failure, but they were the only significant factors identified as associated with extrahepatic failure.

Although data was not shown, we also analyzed the clinical factors related to overall survival. T3/4 stage, Child-Pugh class B, infield failure at 3 months after finishing RT and both the elevation of pre-CCRT AFP levels (≥ 200 IU/ml) and PIVKA-II (≥ 60 mAU/ml) were significant factors in multivariate analysis.

Toxicity during CCRT and the following 3 months has been summarized in Table 4. Neutropenia \geq Grade 3 and thrombocytopenia \geq Grade 3 were observed in 17 and 23 patients, respectively. Five patients had severe gastroduodenal toxicities such as gastritis, duodenitis or an ulcer. Of the 138 patients, 20 had died 3 months after CCRT, and hepatic failure was the cause of death in 13 patients. Hepatic failure seemed to have resulted from complex factors involving treatment and disease progression.

DISCUSSION

Liver-directed therapy, consisting of local radiotherapy and concurrent HAIC, has been demonstrated as prolonging survival in patients with liver-confined HCC [4, 6–9]. Ben-Josef *et al.* performed high-dose 3D-CRT (median 60.75 Gy in 1.5 Gy per fraction, twice daily, range 40–90 Gy) with concurrent HAIC with floxuridine (0.2 mg/kg/day) [9]. Out of 128 patients in their study, 35 had HCC and showed a median overall survival of 15.2 months. Han and Seong *et al.* [4] used concurrent 5-FU HAIC (500 mg/day) and 3D-CRT (45

Table 3. Risk factors of progression-free survival (PFS)

a) Univariate analysis									
	Local failure						Distant failure		
	Infield failure			Intrahepatic-outfield failure			Extrahepatic failure		
	No.	2-year PFS (%)	P-value	No.	2-year PFS (%)	P-value	No.	2-year PFS (%)	P-value
Age (y)									
< 50	37	54.8	0.907	37	26.6	0.309	37	26.2	0.007
≥ 50	101	44.5		101	43.5		101	48.9	
Stage									
II	20	59.8	0.474	20	40.7	0.610	20	60.8	0.116
III-IV	118	46.3		118	40.5		118	40.2	
Portal vein thrombosis									
No	61	55.2	0.233	61	40.6	0.275	61	36.6	0.443
Yes	77	38.5		77	39.3		77	52.3	
Pre-CCRT Treatment history									
Primary treatment group	104	53.5	0.035	104	38.5	0.892	104	41.8	0.314
Recurrence treatment group	34	29.6		34	41.6		34	48.3	
Pre-CCRT AFP (IU/ml)									
< 200	60	43.5	0.916	60	42.7	0.062	60	44.8	0.087
≥ 200	78	53.8		78	38.8		78	43.7	
Pre-CCRT PIVKA-II (mAU/ml)									
< 60	17	51.4	0.962	17	53.2	0.160	17	60.5	0.177
≥ 60	118	44.9		118	36.2		118	40.2	
Pre-CCRT AFP & PIVKA-II									
≥ 200 & ≥60	67	50.3	0.465	67	38.7	0.005	67	42.4	0.003
< 200 &/or <60	68	46.2		68	43.5		68	48.4	

Continued

CCRT for advanced but liver-confined HCC

Table 3. *Continued*

b) Multivariate analysis									
	Local failure			Distant failure					
	Infield failure	Intrahepatic-outfield failure			Extrahepatic failure				
	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
Age	0.742	0.360–1.531	0.420	0.853	0.480–1.518	0.589	0.680	0.382–1.209	0.189
≥ 50									
Stage	1.036	0.431–2.493	0.937	0.878	0.426–1.810	0.724	1.869	0.845–4.134	0.122
III–IV									
Portal vein thrombosis	1.386	0.725–2.651	0.324	1.267	0.729–2.203	0.401	0.669	0.398–1.126	0.131
Yes									
Pre-CCRT treatment history	2.190	1.132–4.235	0.020	1.198	0.677–2.120	0.536	0.858	0.458–1.606	0.631
Recurrence treatment group									
Pre-CCRT AFP (IU/ml)	0.444	0.096–2.048	0.298	1.045	0.231–4.726	0.954	0.242	0.046–1.276	0.094
≥ 200									
Pre-CCRT PIVKA-II (mAU/ml)	0.742	0.250–2.207	0.592	1.422	0.423–4.784	0.569	0.602	0.223–1.622	0.315
≥ 60									
Pre-CCRT AFP & PIVKA-II									
≥ 200 and ≥60	2.511	0.485–12.997	0.272	1.740	0.353–8.587	0.496	6.949	1.219–39.614	0.029

PFS = progression-free survival, CCRT = concurrent chemoradiotherapy, AFP = alpha-feto-protein, PIVKA-II = protein induced by vitamin K absence; HR, hazard ratio; CI, confidence interval.

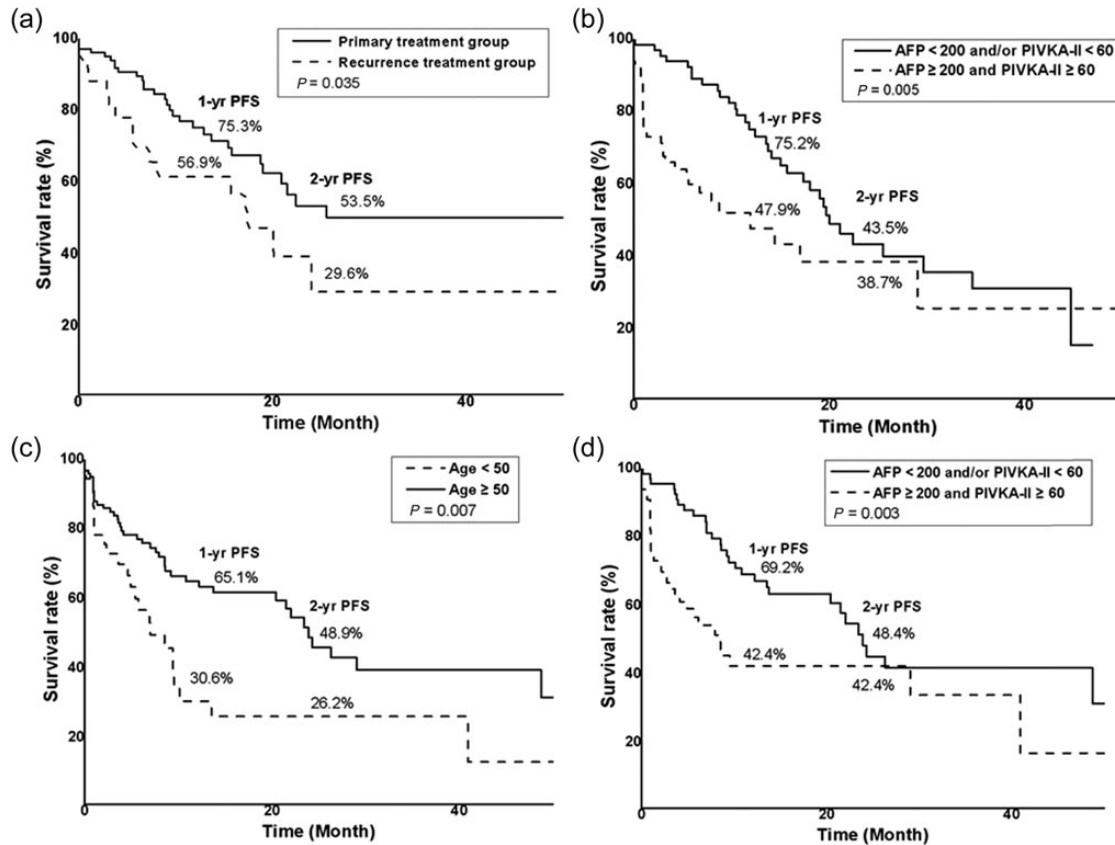


Fig. 3. Progression-free survival (PFS) of treatment failure by risk factor. (a) PFS of infield failure was improved in patients treated with CCRT as the initial treatment (primary treatment group). A history before pre-CCRT treatment was also identified as a significant factor in multivariate analysis ($P = 0.020$). (b) Both the elevation in the pre-CCRT levels of AFP (≥ 200 IU/ml) and PIVKA-II (≥ 60 mAU/ml) were significant factors for intrahepatic-outfield failure. However, changes in the levels of these tumor markers were not significant in multivariate analysis ($P = 0.496$). (c, d) Patients < 50 years of age and with incremental changes in the levels of pre-CCRT AFP (≥ 200 IU/ml) and PIVKA-II (≥ 60 mAU/ml) showed poorer PFS for extrahepatic failure. Incremental changes in the levels of the pre-CCRT tumor marker were the only significant factor identified in multivariate analysis ($P = 0.029$).

Table 4. Toxicity during CCRT and the following 3 months

Toxicity	Grade 3 No. (%)	Grade 4 No. (%)
Neutropenia	14 (10.1%)	3 (2.2%)
Anemia	2 (1.4%)	3 (2.2%)
Thrombocytopenia	21 (15.2%)	2 (1.4%)
AST elevation	19 (13.8%)	8 (5.8%)
ALT elevation	11 (8.0%)	2 (1.4%)
Bilirubin elevation	5 (3.6%)	11 (8.0%)
GI – mucositis, ulcer	5 (3.6%)	0

AST = aspartate transaminase, ALT = alanine aminotransferase, GI = gastrointestinal.

Gy in 25 fractions), followed by monthly HAIC. The median survival time of 40 patients with advanced but liver-confined HCC was 13.1 months and the median for PFS was 6 months. Although lack of a phase III randomized study

excludes this approach as a standard of care for advanced HCC, the therapeutic outcome seems promising with a longer survival time compared with that for sorafenib treatment, suggesting that this would be worthy of active investigation for a subgroup of advanced HCC patients.

In our study, the median PFS was 22.4, 18 and 21.5 months for infield, intrahepatic-outfield and extrahepatic failures, respectively. Intrahepatic-outfield and extrahepatic failures were more common than infield failure. Treatment failure still remains to be overcome, particularly intrahepatic-outfield and extrahepatic failures. We identified several factors influencing each of the three types of treatment failure. A history of pre-CCRT treatment was significantly associated with infield failure. Patients with sufficiently high pre-CCRT serum levels of the two biomarkers AFP and PIVKA-II showed significantly longer PFS.

Patients treated with other modalities before CCRT, most frequently TACE (85.2%), had worse infield PFS. The BCLC guidelines recommend TACE for patients in

intermediate-stage HCC [1]. Currently, TACE is the most popular nonsurgical treatment for HCC in Asia. However, TACE frequently fails to induce complete necrosis, and this may result in residual viable tumor [10, 11]. The mechanism of TACE is extensive ischemic necrosis by hepatic artery obstruction with embolic material. In this process, tissue hypoxia can be induced, which increases expression of angiogenic factor. The latter stimulates the proliferative activity of intratumoral endothelial and tumor cells in the residual HCC after TACE [11, 12], which can further induce resistance to either chemotherapy or radiotherapy. These effects may also facilitate intra- or extrahepatic metastasis. The lung is the most common site of extrahepatic metastasis, and an increased risk of lung metastasis after TACE has been reported. Since vascular endothelial growth factor (VEGF) is a key factor in angiogenesis, an increase in VEGF levels after TACE may induce development of collateral blood vessels, nourishing the surviving residual tumor tissue [10, 13, 14]. A possible relationship between VEGF levels and treatment failure has been investigated in patients treated by TACE [10, 13]. This relationship between VEGF levels and treatment failure might also be relevant in patients treated with CCRT.

In our previous reports, addition of RT improved tumor response and survival both for patients with TACE failure and for patients with incomplete TACE [15–17]. Dose escalation has been considered to increase local control rates [18]. In our study, a history of pre-CCRT treatment was identified as a risk factor for infield failure, suggesting a need for more intensified local treatment for this recurrence treatment group. In this regard, the dose of 45 Gy in our CCRT protocol needs to be escalated according to the patients' subgroup.

Subgroup analysis was done for patients with or without a history of pre-CCRT treatment. Median pre-CCRT AFP levels were 664.5 IU/ml in the primary treatment group and 527.6 IU/ml in the recurrence treatment group, and the median pre-CCRT PIVKA-II levels were 2000.0 mAU/ml and 610.0 mAU/ml, respectively. In the primary treatment group, elevation of AFP and PIVKA-II was a significant factor in outfield and extrahepatic PFS ($P=0.002$ and 0.003 , respectively). However, the factor was not significant in the recurrence treatment group ($P=0.171$ and 0.07 , respectively).

Levels of both AFP and PIVKA-II before CCRT were associated with extrahepatic failure. The serum indicators AFP and PIVKA-II are the most commonly used tumor markers in HCC, and it is well known that an HCC with high levels of AFP and PIVKA-II is associated with more aggressive tumor behavior, e.g. large numbers of tumors, frequent vascular invasion, early intrahepatic and distant metastasis, and poor prognosis [19–21]. In our study, elevation of only one of the biomarkers was not significant for treatment failure, but elevation of pre-CCRT levels of both was significant. As shown in Fig. 3d, differences in the survival curves according to the pre-CCRT tumor markers were marked in

early period of follow-up. Ultimately, difference in PFS seemed to be minimal with longer follow-up. Therefore, pre-CCRT levels of tumor markers could be helpful for predicting early failure.

Since our protocol-based CCRT consisted of local RT and regional chemotherapy through HAIC, a component of systemic treatment was omitted. Our results suggest that systemic treatment is necessary for a subgroup of patients.

In this study, we have identified risk factors for treatment failure: history of pre-CCRT treatment, as a factor associated with infield failure; and elevation of both AFP and PIVKA-II levels before CCRT, as a risk factor for extrahepatic failure. This suggests that more intensified treatment is required for the patients presenting risk factors; intensification of local treatment for those with a past treatment history, and more effective systemic treatment for those with elevated serum tumor markers. Since sorafenib is the only recommended systemic agent at present, a novel approach combining sorafenib and CCRT needs further investigation.

CONCLUSION

Treatment failure was frequent in HCC patients treated with a liver-directed therapy of CCRT, more commonly intrahepatic-outfield and extrahepatic failures than infield failure at 3 months after RT. A history of pre-CCRT treatment, as well as levels of pre-CCRT tumor markers, were identified as risk factors that can predict treatment failure. More intensified treatment is required for the patients presenting risk factors.

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